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TRANSLATOR'S AFFIDAVIT

I, Andrew Wilford, a citizen of the United States of America, residing in Dobbs Ferry, New York, depose and state that:

I am familiar with the English and German languages;

I have read a copy of the German-language document PCT application PCT/DE2004/002689 published 28 July 2005 as WO 2005/068359; and

The hereto-attached English-language text is an accurate translation of this German-language document.



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METHOD OF ENRICHING HYPERPOLARIZED ATOMIC NUCLEI

AND AN APPARATUS FOR IMPLEMENTING THE METHOD

The invention relates to a method of enriching hyperpolarized atomic nuclei and an apparatus for carrying out the method.

Recent developments in magnetic resonance tomography (MRT) and magnetic resonance spectroscopy (NMR) with polarized noble gases anticipate applications in medicine, physics and materials science. Large polarizations of nuclear spins of noble gases may be achieved by optical pumping using alkali atoms, as described in the publication Happer, et al., Phys. Rev. A, 29, 3092 (1984).

Through optical pumping by incident light radiation into matter, the occupation numbers of certain energy states are increased significantly relative to the state of equilibrium. Polarization thereby refers to the degree of orientation (ordering) of the spins of atomic nuclei, or electrons. For instance, 100 percent polarization means that all nuclei or electrons are oriented likewise. Polarization of nuclei or electrons is tied to a magnetic moment.

Hyperpolarized ^{129}Xe is, for instance, inhaled by or injected into a human being. The polarized xenon accumulates 10 to 15 seconds later in the brain. The distribution of the noble gas in the brain is determined by using magnetic resonance tomography. The result is used for further analysis.

Choosing a polarized noble gas depends in each case on its actual application, ^{129}Xe has a great chemical shift. If, for example, xenon is adsorbed on a surface, its resonance frequency changes significantly. Moreover, xenon is soluble in lipophilic liquids. When such properties are desired, xenon is used. The noble gas helium is hardly soluble in liquids. The isotope ^3He is therefore regularly used, when cavities are concerned. The human lung is an example of such a cavity.

Some noble gases exhibit other useful properties. The isotopes ^{83}Kr , ^{21}Ne and ^{131}Xe have a quadruple moment that is of interest, e.g., for experiments in basic research or surface physics. However, these noble gases are very expensive, which makes them unsuitable for applications, in which greater amounts are used.

From the publication Driehuys et al. (Appl. Phys. Lett. (1996). 69, 1668) it is known how to polarize ^{129}Xe in a polarizer in the following way.

Based on a gas supply, a gas flow consisting of a mixture of 1 % ^{129}Xe and N_2 , including 98 % ^4He , is mixed with Rb vapor in a container and conducted through a test cell. Using a laser, circular polarized light is produced, i.e. light in which the spin momentum or the spin of the photons has the same direction. In the test cell, the Rb atoms are optically pumped as an optically pumpable species by the laser beam ($\lambda \sim 795$ nm, Rb D1 line) longitudinally to a magnetic field, thereby polarizing the electron spins of the Rb atoms. The spin momentum of the photons is thereby transferred to the free electrons of the alkali atoms. The spins

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of the electrons of the alkali atoms vary greatly from thermal equilibrium, i.e. the alkali atoms are polarized. Through the collision of an alkali atom with a noble gas atom, the polarization of the electron spins is transferred from the alkali atom to the noble gas atom, whereby polarized noble gas forms. The polarization of the electron spin of the alkali atoms created by optical pumping of alkali atoms is thus transferred through spin exchange of the alkali electron to the nuclear spin of the noble gases.

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Alkali atoms are used, since they possess a large optical moment of dipole, which interacts with light. Furthermore, alkali atoms exhibit a free electron, so that unfavorable interactions between two or more electrons per atom cannot occur.

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The partial pressure of ^4He in the gas mixture is up to 10 bar. Compared with other partial pressures (xenon or nitrogen), this is very high. This relatively high partial pressure means that polarized atoms only rarely reach the test wall of the glass cell and lose their polarization there, e.g., through interaction with paramagnetic centers. With an increasing partial pressure of ^4He , the probability of the polarized atoms hitting the cell wall decreases.

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The heavy noble gas atoms, e.g. xenon atoms, give rise to strong relaxation of the polarization of the optically pumped alkali atoms when colliding with the alkali atoms. In order to retain maximum polarization of the alkali atoms during optical pumping, the partial pressure of the xenon gas in the gas mixture must be correspondingly low. Even with a partial pressure in the

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gas mixture of 0.1 bar, a laser capacity of around 100 Watt is required in order to achieve a polarization of the alkali atoms of about 70 percent in the whole test volume.

For ^{129}Xe , the nuclear-spin polarization formation times are between 20 and 40 seconds due to the high spin exchange of the cross section. Due to the very high rubidium-spin destruction rate for rubidium xenon collisions, the xenon partial pressure may not exceed stated values, so that a sufficiently high rubidium polarization may be maintained during optical spin-exchange pumping. Hence ^4He is employed as a buffer gas in such polarizers to achieve line broadening.

Test cells of glass are employed, blown from one piece, and in which the noble gas atoms or the atomic nuclei are optically pumped.

According to the prior art, the test cell is placed in a static magnetic field B_0 of about 10 Gauss produced by coils, especially a pair of so-called Helmholtz coils. The direction of the magnetic field extends parallel to the cylinder axis of the test cell, or parallel to the direction of the laser beam. The magnetic field serves to guide the polarized atoms. The rubidium atoms, which are optically highly polarized due to the laser light, collide in the glass cell, e.g. with the xenon atoms, and release their polarization to the xenon atoms.

Typical values of partial pressure at the exit of a polarizer are $p_{\text{He}} \sim 7$ bar, $p_{\text{N}_2} \sim 0.07$ bar, $p_{\text{Xe}} \sim 0.07$ bar at a numerical particle density of Rb of $\sim 10^{14} \text{ cm}^{-3}$. With hyperpolarization of ^{129}Xe , its partial pressure is limited during

polarization to about 0.1 bar due to spin-exchange optical pumping. In order to produce a sufficient and satisfactory amount and thickness of hyperpolarized gas for many applications, Xe thickness in the gas needs to be increased for enrichment.

5 A method of enriching hyperpolarized ^{129}Xe is disclosed in European Patent EP 0 890 066 B1. During the process, a gas mixture containing hyperpolarized ^{129}Xe flows through an enrichment reservoir. The reservoir is cooled, e.g. with liquid N_2 to a temperature at which xenon condenses to a frozen state, whereby it
10 is enriched in frozen state in the reservoir from the flowing output gas. Rubidium settles on the wall at the exit of the test cell due to the high melting point compared with the melting points of the other gases. The polarized ^{129}Xe or the residual gas mixture is carried further by the test cell into a freezing unit, which
15 consists of a glass flask, whose end is submerged in liquid nitrogen. The glass flask is situated in a magnetic field with a strength up to 1 Tesla. To obtain long enrichment times of ^{129}Xe of about 1 hour, a magnetic field must be applied on a magnitude of about 1 T, since with weaker magnetic fields and a temperature of
20 liquid N_2 , the relaxation time of the polarized Xe ice is only a few minutes, so that considerable parts of the polarization again decay for long enrichment times. Longer relaxation times ($T_1 \sim$ a few hours) can only be obtained, when the Xe ice is enriched/stored at a temperature of the liquid He of about 4 °K.

25 Disadvantageously, the ^{129}Xe thus needs to be frozen very quickly and preferably without any loss, following polarization, by using a strong magnetic field of about 1 T, stored and subsequently

re-vaporized in Xe gas. Only about 1 to 2 hours remain for using the noble gas, before the xenon polarization through relaxation has declined to such an extent that further use is no longer possible. The complexity of preparing strong magnetic fields and temperatures in order to condense ^{129}Xe makes this process expensive and cumbersome.

5 The object of the invention is to provide a method for enriching hyperpolarized atomic nuclei at a reasonable cost. A further object of the invention is to make available an apparatus 10 for carrying out the method.

This object is attained by a method with the totality of the features of claim 1, and by an apparatus as claimed by the dependent claims. Advantageous embodiments follow from the related 15 claims.

15 The process provides for the solution of hyperpolarized atomic nuclei, flowing in a gas mixture, in a solvent cooled to below 293 K.

20 Solubility is defined as the density of the hyperpolarized gas in the solvent relative to the density of the hyperpolarized gas in the gas chamber situated above a given temperature and pressure. The solubility is also referred to as the Ostwald coefficient.

25 Within the scope of the invention, it was recognized that by using a solvent cooled below room temperature, especially an organic solvent, such as a hydrocarbon, it was possible to obtain a large increase in gas density in the solvent compared to the gas phase. In the solvent cooled below room temperature, a solubility

of at least twice that at room temperature is obtained, which is used for the hyperpolarized atomic nuclei in the solvent.

The solvent below room temperature has an Ostwald coefficient of at least 2 for the hyperpolarized atomic nuclei. With decreasing temperatures, solubility or the Ostwald coefficient increases to values of up to 200. Above room temperature, the Ostwald coefficient may advantageously assume a value below 1.

The method according to the invention is by no means limited to enrichment of hyperpolarized atomic nuclei. Rather, it was found that the process will always be useful when a certain component to be enriched in a gas mixture is especially easily soluble in comparison with other components of the mixture in a solvent cooled below 93 °K.

For example, the enrichment of carbon isotopes ^{12}C and ^{13}C from a mixture of N_2 and O_2 may be mentioned. Following solution in a solvent cooled below room temperature, the carbon isotopes are enriched and separated from N_2 and O_2 . Subsequently ^{12}C and ^{13}C are separated through isotopic separation. Any valuable gas from a mixture may be enriched and possibly separated through further steps of the method. The method has the advantage of being economical and easy to handle.

In a further embodiment of the invention, a lipophilic solvent with high viscosity is chosen for the method.

As solvent for hyperpolarized ^{129}Xe , toluol with a Ostwald coefficient of about 5 is, for example, chosen as the standard conditions (293 °K, 1 bar), or ethanol with an Ostwald coefficient of about 2.5 at standard conditions.

Pentane, acetone/methanol and butanol are generally suitable solvents for enrichment of hyperpolarized noble gases. The solvent may be chosen according to the temperature. In an especially advantageous embodiment of the invention, the solvent is present in liquid phase even at low temperatures, e.g. 5 180 °K.

In a further embodiment of the invention, the melting point of the solvent decreases compared with the pure solvent without the hyperpolarized atomic nuclei.

10 Such a decrease of the melting point was determined within the scope of the invention in the case of toluol, in which ¹²⁹Xe was dissolved.

15 Dissolving hyperpolarized atomic nuclei in the solvent is thus done at temperatures that are lower than expected from prior art. This effect is used for enrichment, since lower temperatures result in a rapid increase of solubility.

As solvents, olive oil and benzol also exhibit a high Ostwald coefficient.

20 A suitable choice of solvent will ensure the desired increase of solubility and thus enrichment of the hyperpolarized atomic nuclei in the solvent.

25 The solvent comprises, for example, ethanol and/or toluol. For both solvents within the scope of the invention, a large solubility below room temperature was determined for hyperpolarized atomic nuclei. It is conceivable that these solvents may be used for enrichment of other components from a gas mixture, such as ¹³C.

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In the case of hyperpolarized atomic nuclei to be enriched, their T_1 relaxation times in the solvent during the process is chosen greater than their residence time in the solvent. Deuterized solvents, such as $C_6D_5CD_3$ (toluol) or CD_3CD_2OD (ethanol), in which the relaxation times of the hyperpolarized atomic nuclei are greater than 100 seconds, may be chosen.

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Dissolving a hyperpolarized noble gas in a solvent from the gas flow of a polarizer is preferably done in a chamber, in which the solvent is either present in cooled condition or is still undergoing cooling. Similarly, other gases to be enriched are conducted into such a chamber.

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The process optionally provides for introducing degassing from the solvent after dissolving a component to be enriched, e.g. a hyperpolarized noble gas. For this purpose, the solvent may be conducted out of the cooling chamber into a further chamber for degassing.

Solution and degassing may conceivably be performed in one and the same chamber, provided the chamber has cooling and heating means.

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The volume of the chambers, especially the chamber in which degassing occurs, is chosen sufficiently large, so that if hyperpolarized atomic nuclei are being enriched, the relaxation times of the nuclei through wall contact is longer at the inner walls than is the enrichment times.

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The T_1 time of hyperpolarized atomic nuclei is determined, e.g. by their interaction with the inner wall of the chamber. By coating the inner walls of the chambers and/or the

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connection lines between the chambers, e.g. with deuterized monochlorosilane or PFA (perfluoroalkoxy compounds), T_1 times exceeding one hour may be obtained. For instance, for Xe gas, a fundamental T_1 (Xe-Xe interaction) time of 56 h/p (amagat) may be applied.

With the method according to the invention hyperpolarized atomic nuclei may therefore be enriched and stored for a longer period than with the known methods.

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During the enrichment process, multiple repetition of the solution and degassing steps of the components to be enriched or the hyperpolarized atomic nuclei in and from a cooled solvent may be done in an especially advantageous manner. Especially, the solvent may be conducted in chambers especially provided for this purpose. This procedure may bring about a pump effect and for enrichment, an increased density of the components to be enriched.

The flow of the solvent may be controlled continuously or semi-continuously via the pressure in the chambers or in the pressure compensation containers or tanks.

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In the case of hyperpolarized ^{129}Xe as a component to be enriched, the process has the advantage that depending on the solvent only minor amounts of N_2 are dissolved in the storage medium, whereas with known freezing methods, considerable amounts of N_2 are frozen.

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An apparatus for carrying out the method therefore comprises at least one chamber with means for degassing the enriched components dissolved in a solvent situated in the chamber.

For the purpose of degassing, the chamber is provided with, e.g. heating coils and/or means for producing ultrasound.

For a hyperpolarized noble gas as a component to be enriched, the apparatus features at least one means for forming a magnetic field with a strength not exceeding 0.04 Tesla, e.g. a Helmholtz coil.

As an advantage, expensive and heavy magnets for generating magnetic fields for the hyperpolarized atomic nuclei are thus no longer needed.

Instead, simple Helmholtz electromagnets, or permanent magnets suffice, since the cooled solvent must be exposed to a maximum magnetic field of only 0.04 Tesla for enrichment. This affects the mobility afforded by such apparatuses.

When solution and degassing occur in the same chamber, the chamber features means for degassing, and possibly cooling.

The method according to the invention enables enrichment of hyperpolarized atomic nuclei at a considerably higher temperature than is used according to prior art. The temperature of the solvent may be set to, e.g. about 180 °K during enrichment, versus 77 °K if condensed Xe-Si is used. The temperature needed for the enrichment method using solvents according to the invention may thus be obtained through standard cooling methods or coolants, e.g. Peltier elements. This advantageously allows for a compact design of the apparatus according to the invention for mobile systems.

If degassing is done in another chamber, the apparatus features at least one chamber, in which the hyperpolarized atomic

5 nuclei or other components to be enriched are dissolved, and a further, second chamber connected with this chamber. The cool solvent containing the gas to be enriched is conducted from the first to the second chamber, where degassing is done. The second chamber thereby has the said means for degassing from the solvent.

10 The apparatus may have a tank for the enriched gas, such as a hyperpolarized noble gas. This tank is connected with the chamber(s) in which degassing is done. The enriched, possibly hyperpolarized gas is introduced into the tank, whereas the solvent is disposed of, or returned under cooling to the cooling chamber. In an especially advantageous embodiment of the invention, the apparatus has at least two units connected successively, each consisting of a chamber, in which the component to be enriched, e.g. a hyperpolarized noble gas is dissolved in a cooled solvent, and a further chamber, in which the solvent is degassed a second time. The solution and degassing process may thus be repeated and carried out in two stages, for example. This advantageously results in a further increase in solubility or enrichment in the solvent.

15 20 The solvent cooled beneath 293 °K may, of course, be used not only for enrichment, but also for storing and transporting a component, e.g. a certain hyperpolarized noble gas, to be enriched. Once enriched, gases, especially hyperpolarized noble gases, are however also of special interest in the cooled solvent, as the method according to the invention is not limited to the above-mentioned advantages. In many applications, it is necessary to make available, e.g. hyperpolarized ^{129}Xe pre-dissolved in a liquid

in order to carry it to the objects or substances to be examined, e.g. complex molecules, or examine the diffusion of liquids in porous structures. The step involving thawing from the Xe ice is advantageously omitted in the method according to the invention. 5 A cooled solvent containing a dissolved hyperpolarized noble gas is therefore a direct contrast agent for magnetic resonance tomographic examinations.

Cooled ethanol or toluol with dissolved ^{129}Xe may be also mentioned as an example.

10 A cool solvent containing hyperpolarized atomic nuclei, or ^{13}C , ^{235}U or ^{238}U , whereby the solvent has a temperature of below 293 K, is therefore of special interest. The solvent may, besides toluol or ethanol, also comprise pentane or other solvents. Such a solvent may

15 The invention is explained in more detail in the following with reference to the examples and attached figures.

FIG. 1 shows measuring results for the solubility of ^{129}Xe in toluol and ethanol depending on the temperature of the solvent.

20 FIG. 2 shows an apparatus for carrying out the method according to the invention.

According to FIG. 1 it appeared surprisingly that already at a temperature of 273 °K, a clear increase of the solubility or Ostwald coefficient of ^{129}Xe is obtained compared to at room temperature.

25 At a temperature of about 240 °K, a ten times higher density of ^{129}Xe compared with the gas phase is already obtained both in ethanol and toluol. An even higher solubility of ^{129}Xe in

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the solvent is obtained by cooling to temperatures of 180 °K, thereby obtaining a 100-fold increase of the density in both toluol and ethanol compared to the gas phase. Further cooling by just a few degrees Kelvin already results in an increase of the Ostwald coefficient to a value of 200 (FIG. 2).

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A further sharp rise of solubility occurs, when the solvent is further cooled. This effect may also be produced with other solvents and hyperpolarized atomic nuclei, or with ¹³C, low temperatures is especially interesting, since with a solution of hyperpolarized atomic nuclei, a reduction of the melting point of the solvent relative to pure solvent without hyperpolarized atomic nuclei can be detected, and is also expected for other solvents.

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A typical enrichment apparatus is shown in FIG. 2. A gas mixture 1 with hyperpolarized atomic nuclei flows from a polarizer (not shown) into a first chamber 2 containing a cooled solvent. Chamber 2 has means for cooling the solvent. The solvent containing the gas mixture is thereby cooled to a temperature T_1 of, e.g. 180 °K.

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The gas components are enriched in chamber 2 according to their solubility in the solvent, and thus separated from one another. The unnecessary components of the mixture are released through valve 3. The solvent enriched with the hyperpolarized atomic nuclei is guided through a connection line out of chamber 2 into a further chamber 5. Chamber 5 comprises means for degassing, such as an apparatus for producing ultrasound and/or heating. Degassing of the solvent therefore occurs as a result of heat and/or ultrasound in chamber 5.

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Chamber 5 thus represents a degassing chamber 5 for the hyperpolarized atomic nuclei from the solvent. In chamber 5, a gas pressure of the originally dissolved gas arises due to the degassing of the hyperpolarized atomic nuclei via the solvent. The gas pressure is determined by the partial pressure of the hyperpolarized atomic nuclei (gas component) in solvent chamber 2, and the ratio of the solubilities of this gas component in the solvent at temperatures T_1 in chamber 2 and T_2 in chamber 5.

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The volume of degassing chamber 5, into which the solvent is guided, is sufficiently large in order to ensure a long T_1 relaxation time of the hyperpolarized nuclei. The volume is dimensioned such that a gas pressure of about 2 bar is set. Following degassing in chamber 5, the solution and degassing process may be repeated, as represented in FIG. 2 by continuous lines. For this, starting from chamber 5 at the end of the first enrichment stage, the gas with the hyperpolarized atomic nuclei is guided into chamber 6, where it is cooled to the temperature T_1 . Following enrichment in the solvent, the gas is conducted into chamber 8 with a temperature of T_2 for degassing. Chamber 8, again, has a sufficient volume.

Chamber 6 is provided with a cooling unit 7 for cooling the solvent, as is chamber 2.

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The respective temperatures T_1 and T_2 in chambers 2, 6, as well as 5, 8, may but need not be identical. Instead, the chambers may be provided with heating apparatuses and means for producing ultrasound, depending on the actual application. The degassed

hyperpolarized atomic nuclei are guided from chamber B into a tank 9.

The inner walls of the tank 9 are lined with PFA or monochlorosilane in order to prolong the relaxation time of the hyperpolarized atomic nuclei. Basically, all chambers and connecting lines of the apparatus may be designed like this. The solvent is fed into a waste container 14 and disposed of, or stored temporarily for reuse in a container 10. The transport may be controlled by the gas pressure by exposing the solvent to pressure compensation, e.g. in container 10. The waste container 14 is arranged behind either chambers 5 or 8 for degassing. Subsequently, the solvent is returned through a cooling coil via connecting line 12 to chamber 2.

A storage tank 13 containing solvent is arranged before the cooling coil 11, so that spent solvent is replaced and may be pre-cooled to the intended temperature T_1 .

The complete process may be controlled continuously or semi-continuously via the pressure tank 9 and pressure compensation container 10.

The process may be controlled at least partially via the drawn valves. Additional valves not shown may be arranged, e.g. behind chamber 8 before the branching off after waste container 14. The process may also be performed in one step, as indicated in FIG. 2 by the dotted lines. Then, valves that are not shown ensure that the solvent released from chamber 5 may be fed into the pressure compensation container 10, or else an equivalent three-way valve may be inserted before the pressure compensation container.

To store the gas in tank 9, a magnet field below 0.01 T need only be provided, whereby Helmholtz coils are appropriately arranged as a part of the apparatus.

5 The following ^{129}Xe densities in the solvent (toluol/ethanol) may be set at different temperatures:

	Stage 1 (Chamber 2)	Stage 2 (Chamber 6)
T = 240 °K,	p _{Xe} ,Sol -0.7 bar	~3.5 bar
T = 200 °K,	p _{Xe} ,Sol -2.1 bar	~10 bar
10 T = 180 °K,	p _{Xe} ,Sol -7.0 bar	~20 bar

Similar values are obtained for pentane, acetone, methanol and other solvents.

Naturally, another valuable gas may be enriched, e.g. ^{13}C , using such an apparatus.